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A pilot study utilizing whole body 18 F-FDG-PET/CT as a comprehensive screening strategy for occult malignancy in patients with unprovoked venous thromboembolism[☆]

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Abstract

Background—Approximately 7–10% of patients with unprovoked VTE will be diagnosed with cancer within 12 months. Although cancer screening has been proposed in these patients, the optimal strategy remains unclear. In a pilot study, we prospectively investigated the use of FDG-PET/CT to screen for occult malignancy in 40 patients with unprovoked VTE.

Materials/Methods—Patients were initially screened for occult malignancy with a focused history, physical, and laboratory evaluation. Patients underwent whole body FDG-PET/CT and were followed for up to two years for a new diagnosis of cancer. The total costs of using FDG-PET/CT as a comprehensive screening strategy were determined using 2010 Medicare reimbursement rates.

Results—Completion of FDG-PET/CT imaging was feasible and identified abnormal findings requiring additional evaluations in 62.5% of patients. Occult malignancy was evident in only one patient (cancer incidence 2.5%) and FDG-PET/CT imaging excluded malignancy in the remainder of patients. No patients with a negative FDG-PET/CT were diagnosed with malignancy during an average ($\pm$ SD) follow-up of 449 ($\pm$ 311) days. The use of FDG-PET/CT to screen for occult malignancy added \$59,151 in total costs (\$1,479 per patient). The majority of these costs were due to the cost of the FDG-PET/CT (\$1,162 per patient or 78.5% of total per-patient costs).

Conclusions—FDG-PET/CT may have utility for excluding occult malignancy in patients with unprovoked VTE. The costs of this comprehensive screening strategy were comparable to other

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Conflict of Interest Disclosures

The authors have no relevant financial conflicts of interest to disclose.

screening approaches. Larger studies are needed to further evaluate the utility and cost-effectiveness of FDG-PET/CT as a cancer screening strategy in patients with unprovoked VTE.

Keywords

Cancer Screening; FDG-PET/CT; Occult Malignancy; Venous Thromboembolism; Cost Effectiveness; Early Detection of Cancer

Introduction

An association between clinically evident venous thromboembolism (VTE) and occult cancer has been recognized for decades. Although precise estimates vary, around 7 to 10% of patients with idiopathic VTE are diagnosed with cancer in the twelve months following the index VTE [1-4]. Given the apparent risk of occult malignancy in patients with acute, unprovoked VTE, cancer screening is an important consideration in these patients.

Although retrospective data suggests that limited cancer screening, including a careful medical history and physical examination and routine laboratory studies, may be sufficient, prospective studies provide some support for more comprehensive (or “extensive”) screening, particularly in select patients. A variety of screening strategies have been studied, including the use of extensive laboratory testing and more extensive diagnostic imaging with ultrasound and computed tomography (CT) [5-10]. Unfortunately, universal agreement with regards to the optimal screening approach is lacking.

The cost-effectiveness of these extensive cancer screening strategies also remains controversial. Depending on the strategy utilized, some approaches may be more cost-effective than others. As one example, Di Nisio and colleagues, using data from the SOMIT trial, suggested that CT imaging of the abdomen and pelvis with or without mammography along with sputum cytology is cost effective in patients with idiopathic VTE [11].

A relatively newer imaging modality that may be very effective at identifying or excluding occult malignancy in patients with idiopathic VTE is whole body ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). FDG-PET combined with CT appears to be more sensitive than each individual imaging test for identification of malignancy [12-16]. Nevertheless, the utility and cost-effectiveness of whole-body FDG-PET/CT to screen for occult malignancy in patients with unprovoked VTE has not been prospectively studied. In a pilot study, we prospectively studied the feasibility of using whole body FDG-PET/CT as a comprehensive cancer screening strategy in patients with unprovoked VTE.

Methods

Study Cohort

This was a prospective cohort follow-up study of patients referred to a university tertiary-care referral center. The primary aim of this study was to determine the feasibility of performing FDG-PET/CT to screen for occult malignancy in patients with unprovoked VTE. The local institutional review board approved this study. We actively screened all admissions to the hospital for VTE and all patients diagnosed with VTE in the vascular laboratory during compression ultrasounds. Consecutively identified patients meeting inclusion criteria and providing informed consent were included in the study. Patient inclusion criteria were: symptomatic, unprovoked VTE, including proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) diagnosed within one month of FDG-PET/CT imaging. Proximal DVT was diagnosed using Doppler ultrasound to identify an area of non-compressibility in one or more proximal veins of the lower extremity, including

the femoral, iliac, and popliteal veins. PE was diagnosed using CT pulmonary angiography (CTPA) based on the finding of one or more intraluminal filling defects in a segmental (or more proximal) pulmonary artery. All VTE was objectively confirmed by imaging prior to study enrollment.

Exclusion criteria included isolated distal DVT, upper extremity DVT, current pregnancy (all female patients of childbearing age underwent a serum beta-HCG (human chorionic gonadotropin) test prior to enrollment), and provoked VTE. Distal DVT was defined as non-compressibility of one or more vein segments below the popliteal vein. Provoked VTE was defined as VTE occurring in the setting of known thrombophilia, known active cancer, current pregnancy or the postpartum period, use of estrogen, thalidomide, or VEGF inhibitor, surgery or hospitalization within four weeks, recent immobility, the presence of an indwelling vascular device such as a PICC, or severe varicose veins.

Screening for Malignancy

All consenting patients underwent a focused evaluation for evidence of occult malignancy using a standardized format prior to completion of the FDG-PET/CT imaging. This evaluation included a comprehensive history, physical examination, and laboratory evaluation (including a complete blood count, urinalysis, and liver-and renal-function testing). Whether or not age-appropriate cancer screening had been completed by study participants prior to enrollment was recorded, but was not performed as part of our study protocol.

Thrombophilia Testing

Patients were tested for inherited thrombophilia using a national reference laboratory (www.aruplab.com). Testing included the Factor V Leiden mutation (by PCR and fluorescence monitoring), total homocysteine level, the presence of the prothrombin nucleotide 20210G/A gene mutation, the presence of cardiolipin antibodies (IgG and IgM), and activated protein C resistance. Testing was completed using standard reagents and in accordance with manufacturer protocols.

Acquisition of FDG-PET/CT Images

Patients without cancer identified during the focused evaluation for evidence of occult malignancy were eligible for the extensive screening strategy with FDG-PET/CT. Prior to injection of FDG, subjects fasted for 6 hours, and fasting serum glucose was measured and was confirmed to be ≤ 200 mg/dL. Patients were injected intravenously at a site remote from the symptoms of VTE with 10–15 mCi 18 F FDG and then rested quietly for 90 minutes before scanning. Using a Siemens Biograph 4 tomograph, a PET/CT scan was performed using diagnostic dose modulation CT technique with oral barium-based contrast from mid-forehead through the knees. Intravenous iodinated contrast was not administered. Images were displayed and reviewed as axial, coronal and sagittal attenuation corrected and non-attenuation corrected PET only images, CT only images, attenuation-corrected fused PET/CT images, and PET 3D maximum intensity projections (MIP) images.

Evaluation and Management of Abnormal FDG-PET/CT Images

The FDG-PET/CT images were reviewed collaboratively by a nuclear radiologist and a nuclear medicine physician with expertise in PET/CT (KAM, JMH) who were blinded as to the patient's clinical information. Findings suspicious for possible malignancy were defined as abnormal morphology, opacity or masses (CT) or foci of non-physiological hypermetabolism (PET) not attributable to areas of vascular thrombosis or acute pulmonary infarcts (which may show increased FDG uptake). Society/organ specific guidelines were

followed in documenting “incidental” or “nonspecific findings”, such as pulmonary nodules, adrenal nodules and ovarian cysts. The resulting FDG-PET/CT reports were also reviewed by two clinicians, blinded to clinical data, who independently coded them as either positive or negative for possible malignancy. Abnormal or suspicious findings were independently adjudicated with differences resolved through discussion and consensus.

After reviewing the reports, study clinicians then informed the patient and referring physician of the results of the FDG-PET/CT. When appropriate, patients were referred to subspecialists for further evaluation. Recommendations for further evaluation of suspicious findings were provided. The decision to perform the recommended evaluation was made by the patient and his/her primary care provider.

Statistical Analyses

Proportions and their 95% confidence intervals (CI), when appropriate, were calculated (version 11.0, StataCorp, College Station, TX 77845). There were no differences between the coding of the two, blinded clinicians with regard to whether FDG-PET scans were positive or negative for findings suspicious for malignancy. There were also no differences between the radiologists and the clinicians with regard to the presence of findings suspicious for malignancy. The inter-rater reliability (Cohen’s Kappa) for these comparisons was 100% ($\kappa=1.0$).

Follow-up and Outcomes

Patients were assessed every 3 months for up to two years during structured telephone and/or clinic visits using standard questionnaires to assess for the development of cancer, recurrent VTE, and for all-cause mortality. If cancer was suspected, further appropriate testing was performed according to the patient’s provider(s). For patients who died during the follow-up period, information on the date and cause of death, as well as any information on malignancy found at autopsy (if performed) were recorded. All events were independently confirmed through review of medical records and structured interviews with patients and/or their providers.

Malignancy Classification

If cancer was diagnosed, the type and stage of cancer was recorded using the TNM-scoring system and confirmed through independent review of histological findings (if obtained) or imaging and laboratory results. Occult malignancy was defined as histology-confirmed malignancy not known to be present at the time the VTE occurred but identified either during FDG-PET/CT imaging or subsequent evaluation and follow-up.

Cost Analyses

Costs of the FDG-PET/CT and any additional diagnostic evaluations following FDG-PET/CT were determined using average Medicare reimbursement rates for the year 2010. The cost analysis focused on direct medical costs incurred to resolve suspicious findings made by FDG-PET/CT. Although the cost of the FDG-PET/CT screening scan was covered in this study by a research grant, the national Medicare rate for FDG-PET/CT was included in the cost analysis for the purpose of generalization. The total costs and average cost-per-patient were determined and reported in the US dollar.

Results

During the study period of November 2008 through January 2010, 65 patients were assessed for study participation. Forty-three patients met inclusion criteria, provided informed consent, and were prospectively enrolled in the study. Two patients withdrew consent prior

to completion of the FDG-PET/CT imaging. One patient moved out-of-state prior to completion of the FDG-PET/CT imaging and was not included in the analyses. Our final study population consisted of 40 patients who completed initial screening, FDG-PET/CT imaging, and follow-up.

The average age ($\pm$ SD) was 55 ($\pm$ 14) and 48% of patients were female (Table 1). The initial type of VTE was DVT in 16 patients (40%), PE in 20 patients (50%), and DVT with PE in 4 patients (10%). Thrombophilia testing was completed on 85% ($n=34/40$) of patients. The most common thrombophilias were hyperhomocysteinemia (11.8%) and heterozygosity for the Factor V Leiden mutation (11.8%, Table 2).

All patients received optimal treatment for acute VTE with parenteral anti-thrombotic therapy followed by at least 6 months of oral anticoagulation. The average duration ($\pm$ SD) of anticoagulation was 283 ($\pm$ 185) days and 60% of patients ($n=24$) remained on anticoagulation at the time of last follow-up. The average duration ($\pm$ SD) of follow-up was 449 ($\pm$ 311) days.

During the initial screening evaluation, 16 patients (40%) had ≥ 1 positive clinical findings concerning for underlying malignancy. The most common symptoms were unexplained epigastric pain, fatigue, and changes in bowel or bladder function, and laboratory evaluations identified unexplained microcytic anemia or hypoalbuminemia in a minority of patients (Table 3).

Twenty-five patients (62.5%) had ≥ 1 abnormality on FDG-PET/CT suspicious for malignancy, including pulmonary nodules, enlarged and/or abnormal appearing mediastinal, abdominal, or pelvic lymph nodes, and thyroid nodules (Table 4). Based on these abnormal findings, 37 additional diagnostic evaluations were recommended, and in 21 patients (84%) 2 or more follow-up studies were recommended. The most common additional diagnostic test was follow-up CT of the chest, abdomen, and/or pelvis (38% of all recommended tests), to establish stability or resolution of a finding. Other tests included thyroid ultrasound, MRI of the abdomen, image-guided biopsy, colonoscopy, bronchoscopy and esophagogastroduodenoscopy (EGD) (Fig. 1). There were no diagnostic procedure-related complications. Of the 16 patients with positive clinical findings (Table 3), 13 (81.2%) had one or more abnormalities on FDG-PET/CT requiring additional evaluation, and five (31.3%) had 2 or more suspicious findings on FDG-PET/CT. These were most commonly pulmonary nodules ($n=4$) and abnormal appearing or enlarged lymph nodes ($n=4$), either in isolation or in combination with other findings. Although whole body FDG-PET/CT identified a number of abnormal findings consistent with occult malignancy (Table 4), and patients were followed for an extended period of time, only one patient in this cohort was diagnosed with cancer (cancer incidence 2.5%, 95% CI: 0.6%-12.9%). All of the additional work-ups were negative for malignancy, although other morbid processes and diseases were identified that directly resulted in clinically significant management changes. Patients without evidence of malignancy following completion of FDG-PET/CT and any recommended studies remained free of any cancer diagnosis during the follow-up period.

The patient who was diagnosed with cancer was a 70 year old Caucasian female who presented with saddle pulmonary embolism with right ventricular dysfunction and extensive bilateral DVT. She had recently developed unexplained abdominal pain (with a normal EGD) and unintentional weight loss of 40 pounds (weight on presentation 48 kg, BMI 20 kg/m²) but had not been evaluated for her symptoms prior to hospitalization for acute PE. The CT pulmonary angiogram (CTPA) identified a mildly enlarged mediastinal lymph node (1.5 cm) but there were no palpable abdominal masses or lymphadenopathy on physical examination and routine laboratory tests were unremarkable. FDG-PET/CT revealed a

6.9×3.9 cm lobular, hypermetabolic pancreatic mass with associated periaortic, perihilar, and subcarinal hypermetabolic lymphadenopathy (Fig. 2). Upon review, this pancreatic mass was extensive enough to be visible on the CT portion of the study. Stage IV pancreatic adenocarcinoma was subsequently confirmed by endoscopic ultrasound-guided biopsy. She received palliative chemotherapy with Gemcitabine and died 14 months after study enrollment.

In total, two patients died during the follow-up period (mortality rate 5.0%). In addition to the patient who died from pancreatic cancer, a second patient died from chronic interstitial lung disease approximately 2 months after the index VTE. Two patients (5.0%) had recurrent nonfatal VTE during the follow-up period. One patient had a recurrent, symptomatic, proximal, lower extremity DVT that occurred 16 months following the index DVT and 8 months after anticoagulation was discontinued. A second patient developed recurrent, symptomatic PE approximately 12 months following the index event (DVT with PE) and 6 months after anticoagulation was discontinued. Recurrent VTE did not occur during the follow-up period in any patient identified as having an inherited thrombophilia.

Using 2010 average Medicare reimbursement rates, the estimated total costs for our screening strategy, including the cost of FDG-PET/CT imaging and subsequent diagnostic testing and follow-up of suspicious findings, was \$59,151 (\$1,479 per-patient). The majority of these costs (98%) were due to diagnostic imaging and interventions. The cost of the initial whole body FDG-PET/CT screening study (\$1,162) accounted for 78.5% of all these per-patient costs.

Discussion

Up to 10% of patients with unprovoked VTE will be subsequently diagnosed with cancer and in all patients, age-appropriate cancer screening is recommended [1-4]. In selected patients, a comprehensive cancer screening strategy may be considered. Prior clinical investigations have studied the utility and cost of various screening strategies, including the incorporation of cancer biomarkers, ultrasound, and CT imaging [5-10]. Nevertheless, controversy exists with regard to how extensive the assessment should be and whether it is cost-effective.

FDG-PET/CT is more sensitive than other imaging modalities for detection of malignancy [16,17] and systematically evaluates the majority of the body. As a result, whole body FDG-PET/CT may be a single, comprehensive imaging strategy for the early detection of malignancy in patients with acute, unprovoked VTE. While these data represent a small, pilot study, to our knowledge this is the first prospective investigation utilizing FDG-PET/CT as a comprehensive cancer screening strategy in patients with unprovoked VTE. In our study, FDG-PET/CT was feasible and no patients with a negative FDG-PET/CT scan were diagnosed with malignancy during the follow-up period. Not unexpectedly, and likely due to its enhanced sensitivity, we found that whole body FDG-PET/CT resulted in the identification of suspicious findings requiring additional evaluations in 62.5% of our patients.

While many of these false positive findings were clinically significant, such as the identification of sites of infection or inflammatory diseases, other findings simply represented physiological variants. The necessity of further diagnostic evaluation for these false positive findings does carry potential risks as tests such as bronchoscopy or biopsy are associated with inherent procedural complications. Nevertheless, other studies utilizing colonoscopy, mammography, and CT scans as extensive cancer screening strategies in patients with unprovoked VTE have also reported that false positive test results are not

uncommon [8,9]. Fortunately, and also consistent with these published studies, none of our patients suffered an adverse event related to the additional diagnostic testing. We did not assess the psychological impact of false positive test results on patients, but measurement of these effects may be considered for future studies.

Although a negative FDG-PET/CT scan reduces the likelihood of occult malignancy, some cancers are poorly FDG avid and may fail to be identified by PET. These include low grade lymphomas, low grade breast cancers (such as lobular and tubular types), hepatocellular carcinoma, low grade lung cancers (such as bronchoalveolar carcinoma and carcinoid tumors), hepatocellular carcinoma, renal cell carcinoma, prostate cancer and some testicular cancers [14,16]. Hematological malignancies may escape detection by PET, particularly because of great variability in the degree of metabolic activity displayed by red marrow-containing portions of the skeleton. Furthermore, with many tiny tumors ($\leq 1-2$ cm in diameter), increased metabolic activity may not be identified by FDG-PET/CT because of partial volume effects [14,16].

To minimize the risk to patients, the CT scan performed in conjunction with the FDG-PET study was done with diagnostic exposure parameters and the inclusion of oral barium contrast medium, but was not performed with iodinated contrast. The lack of IV contrast could limit characterization of renal cysts, non-FDG avid hepatic and pancreatic masses, and some lymph nodes, particularly those in the pulmonary hila and mesentery. As such, a negative FDG-PET/CT scan in a patient with signs or symptoms strongly concerning for malignancy may not preclude further diagnostic workup or follow-up as clinically appropriate.

Finally, the initial FDG-PET/CT screening study and any follow-up CT scans do carry some risk due to the long term effects of radiation exposure. Two-thirds of the radiation dose of FDG-PET/CT is derived from the CT scan. Whole body FDG-PET, when performed with a diagnostic quality CT scan, provides a total body effective dose of radiation exposure of 19–40 rem (.19-.40 Sv), depending on the size of the patient and the number of CT detectors [14]. This is equivalent to approximately 6–14 years of natural background radiation. Conservative epidemiological data suggested an increase in cancer risk of 5% with exposure to medical radiation sources with a 1 Sv dose [16,18,19]. Although the risk from radiation exposure from a single FDG-PET/CT is considered low, the cumulative effects of multiple radiographic studies in a given patient may be significant and any unnecessary radiation exposure should be avoided.

The incidence of malignancy in our study (2.5%, 95% CI: 0.6%-12.9%) was slightly lower than reported in other studies utilizing various types of comprehensive cancer screening in patients with idiopathic VTE [5,7,9,10]. This may be due, in part, to the younger cohort of patients in our study and the higher incidence of malignancy in older subjects [10]. In the SOMIT trial, the average age of patients was 66 years [8]. The average age of patients in our study was 55 years with 65% of our patients being 60 years of age or younger. Although the overall incidence of malignancy in the SOMIT trial was 13.1%, the incidence was only 4.9% in patients ≤ 60 years [8].

The average age of subjects in the current cohort is very consistent with other cohorts of patients with unprovoked VTE that have been reported in the literature [20-22]. Additionally, thrombophilia, including the factor V Leiden mutation and the prothrombin gene mutation, was identified in about 18% of subjects, consistent with published studies investigating the prevalence of thrombophilia in unprovoked VTE [8,23]. The prevalence of hyperhomocysteinemia in the current cohort was about 12%, similar to other epidemiologic reports [24].

As age is an important risk factor for malignancy, a comprehensive cancer screening approach may be more effective when applied to older patients with unprovoked VTE. For example, based on the data from the SOMIT trial [8], in patients with unprovoked VTE aged >60 years, the number of patients needed to screen extensively to identify one malignancy was approximately 6. In comparison, in patients with unprovoked VTE aged 51–60, the number needed to screen increases to approximately 19 [8]. Although the use of FDG-PET/CT in our study cohort identified only one occult malignancy, the application of whole body FDG-PET/CT as a comprehensive cancer screening strategy may have higher utility in older patients.

The estimated cost of FDG-PET/CT (\$1,162) and the cost of subsequent diagnostic tests and procedures to resolve suspicious FDG-PET/CT image findings was \$1,479 dollars per patient. The majority of these costs were related to the cost of the initial FDG-PET/CT (78.5%). We used 2010 Medicare figures for our cost analysis and these costs are therefore very conservative. For private insurance or self-paying patients, these costs may be substantially higher. These costs, however, might be mitigated by the use of stringent guidelines defining what incidental findings do and do not require additional diagnostic evaluation [25]. Although published costs of cancer screening strategies in patients with idiopathic VTE vary depending on the strategy used, our costs are similar to data from the SOMIT trial [11] and reasonable when compared to other cancer screening programs [26,27].

The strengths of the current study include the prospective design, the long follow-up period, and the screening process for malignancy prior to acquisition of the FDG-PET/CT. The primary weakness of this study was the small number of patients included in the analysis. However, this was a pilot study designed to test the feasibility of FDG-PET/CT as an extensive cancer screening strategy in patients with unprovoked VTE and was not powered for clinical outcomes. The inclusion of 6 patients (14.6%) with a prior history of VTE may be considered a limitation. While none of these patients had a known history of thrombophilia, a possible predisposition toward thrombosis might have made occult malignancy less likely in these 6 patients. In spite of this, the single patient in whom malignancy was confirmed had a remote history of provoked DVT 15 years prior to her presentation with acute PE and enrollment into this study.

Conclusions

These pilot data represent the first prospective study to investigate the feasibility of using whole body FDG-PET/CT to screen for occult malignancy in patients with unprovoked VTE. In our study cohort, FDG-PET/CT was feasible and safe and none of the patients with a negative FDG-PET/CT scan developed malignancy during an average follow-up of 439 days. The costs of this comprehensive screening strategy were comparable to other screening approaches. Nevertheless, larger studies are needed to further evaluate the utility and cost-effectiveness of FDG-PET/CT as a cancer screening strategy in patients with unprovoked VTE.

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Abbreviations

VTE	venous thromboembolism
FDG-PET	¹⁸ F-fluoro-2-deoxy-D-glucose positron emission tomography
DVT	deep vein thrombosis
PE	pulmonary embolism
CTPA	computed tomography pulmonary angiography
MIP	maximum intensity projections

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Fig. 1.
Diagnostic evaluations performed to resolve findings on FDG-PET/CT.

Fig. 2.

Left Panel. Transaxial fused 18 F-FDG PET/CT scan of the abdomen demonstrates a hypermetabolic mass in the head of the pancreas (arrow). At biopsy, pancreatic adenocarcinomas was demonstrated. Right Panel. Transaxial fused 18 F-FDG PET/CT scan of the abdomen demonstrates a large hypermetabolic lymph node (arrow) just inferior to the primary tumor in the head of the pancreas.

Table 1

Characteristics of the study cohort (BMI: body mass index; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism).

	Number ($\pm$ SD)
<i>Demographics</i>	
Age (years)	55 ($\pm$ 14)
Female, n (%)	19 (48)
Caucasian, n (%)	37 (93)
Weight (kg)	89.1 ($\pm$ 25.1)
BMI (kg/m ²)	29.7 ($\pm$ 8.7)
<i>Type of Index VTE, n (%)</i>	
DVT without PE	16 (40)
PE alone	20 (50)
PE with DVT	4 (10)
<i>Medical Comorbidities, n (%)</i>	
Diabetes Mellitus	3 (7.5)
Current or Past Smoker	11 (27.5)
Inflammatory Arthritis	3 (7.5)
Chronic Lung Disease	1 (2.5)
Prior VTE	6 (15)
History of Malignancy	3 (7.5)

Table 2

Thrombophilia Test Results (n=34 patients evaluable, *defined as a serum homocysteine level >20 $\mu\text{mol/L}$, for both male and females).

	Number	Percentage
Hyperhomocysteinemia*	4	11.8
Factor V Leiden Heterozygosity	4	11.8
Prothrombin Gene Mutation	2	5.9
Anticardiolipin IgG or IgM Antibodies	0	0
Beta-2-Glycoprotein IgG or IgM Antibodies	0	0

Table 3

Clinical findings suspicious for occult malignancy identified in the study population (patients may have ≥ 2 findings and thus the total number may exceed 16).

	Number with clinical finding	Percentage
<i>Symptoms</i>		
Fever or Night Sweats	4	10.0
Unintentional Weight Loss	2	5.0
Fatigue	5	12.5
Change in Bowel or Bladder Habits	5	12.5
Bleeding	3	7.5
Cough, Hoarseness, Hemoptysis	4	10.0
Epigastric Pain	6	15.0
Non-healing Skin Ulcers, Lesions, or Rash	1	2.5
<i>Abnormal Labs</i>		
Microcytic Anemia	2	5.0
Hypoalbuminemia	2	5.0
<i>Abnormal Physical Exam</i>		
Peripheral Lymphadenopathy	1	2.5
Abdominal Mass	1	2.5
Skin Lesion	1	2.5
Enlarged Prostate	1	2.5

Table 4

Whole body FDG-PET/CT identified findings suspicious for occult malignancy in 62.5% of patients.

Abnormality	Number	Percentage
<i>Hypermetabolic thyroid nodule</i>	11	27.5
<i>Hypermetabolic lymphadenopathy</i>	10	25
<i>Lung nodule, with or without hypermetabolism</i>	11	27.5
<i>Abdominopelvic mass or nonphysiologic focus of hypermetabolism</i>	4	10.0
<i>Focal hypermetabolism in esophagus</i>	1	2.5
<i>Focal hypermetabolism in mouth</i>	1	2.5